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Assessment of Second and Third Generation Oral Contraceptives APC Resistance by a Newly Validated ETP-Based APC Resistance Assay

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ASSESSMENT OF SECOND AND THIRD GENERATION ORAL CONTRACEPTIVES APC RESISTANCE BY A NEWLY VALIDATED ETP-BASED APC RESISTANCE ASSAY. A PILOT STUDY.

BACKGROUND

- ❖ ETP-based APC resistance has been identified as a marker of the prothrombotic state observed in women taking combined oral contraceptives (COCs) and figures as a requirement for the investigation of steroid contraceptives.¹
- ❖ In absence of any standardized procedure and validated methodology, which impers a proper study-to-study comparison, the development of a test validated against regulatory standards, is required.²

AIM

To assess the sensitivity of a newly developed and validated ETP-based APC resistance assay in plasmas from healthy volunteers and from women using COCs.

METHOD

- ❖ Resistance to APC was assessed on the Calibrated Automated Thrombogram (CAT) with the Thrombinoscope software, using commercially available CE-marked thrombin generation dedicated kit reagents from Diagnostica Stago.
- ❖ A total of 37 volunteers (FV Leiden negative) aged from 18-35 years were enrolled and stratified into several subgroups:
 - Men (n=16)
 - Women not using hormonal contraception (no COC) [n=9]
 - Women using second-generation COC (2G COC) [n=7]
 - Women using third-generation COC (3G COC) [n=5]
- ❖ These subgroups have been compared based on their APC resistance values expressed in inhibition percentage (%) of the ETP.
- ❖ Inhibition % of the ETP represents the comparison between the ETP measured in presence and in absence of a defined amount of exogenous APC. This ratio (%), subtracted to 100%, gives the inhibition % :
 - $\text{Inhibition \%} = 100\% - \frac{\text{Sample ETP (+APC)}}{\text{Sample ETP (-APC)}}$

RESULTS

The demographic characteristics (age and BMI) of the four groups were well matched (p-value > 0.05).

A. Thrombin generation

- ❖ **In absence of APC**
 - In women not using hormonal contraception, thrombin generation was slightly higher (ETP \pm SD = 1247 \pm 236.6 nm.min) but not significant compared to men (ETP \pm SD = 1172 \pm 151.8 nm.min).
 - In women taking COC (ETP \pm SD = 1758 \pm 316.3 nm.min), we observed significant increase of thrombin generation compared to men (p-value < 0.0001) and women not using hormonal contraception (p-value < 0.001). [► Figure 1]

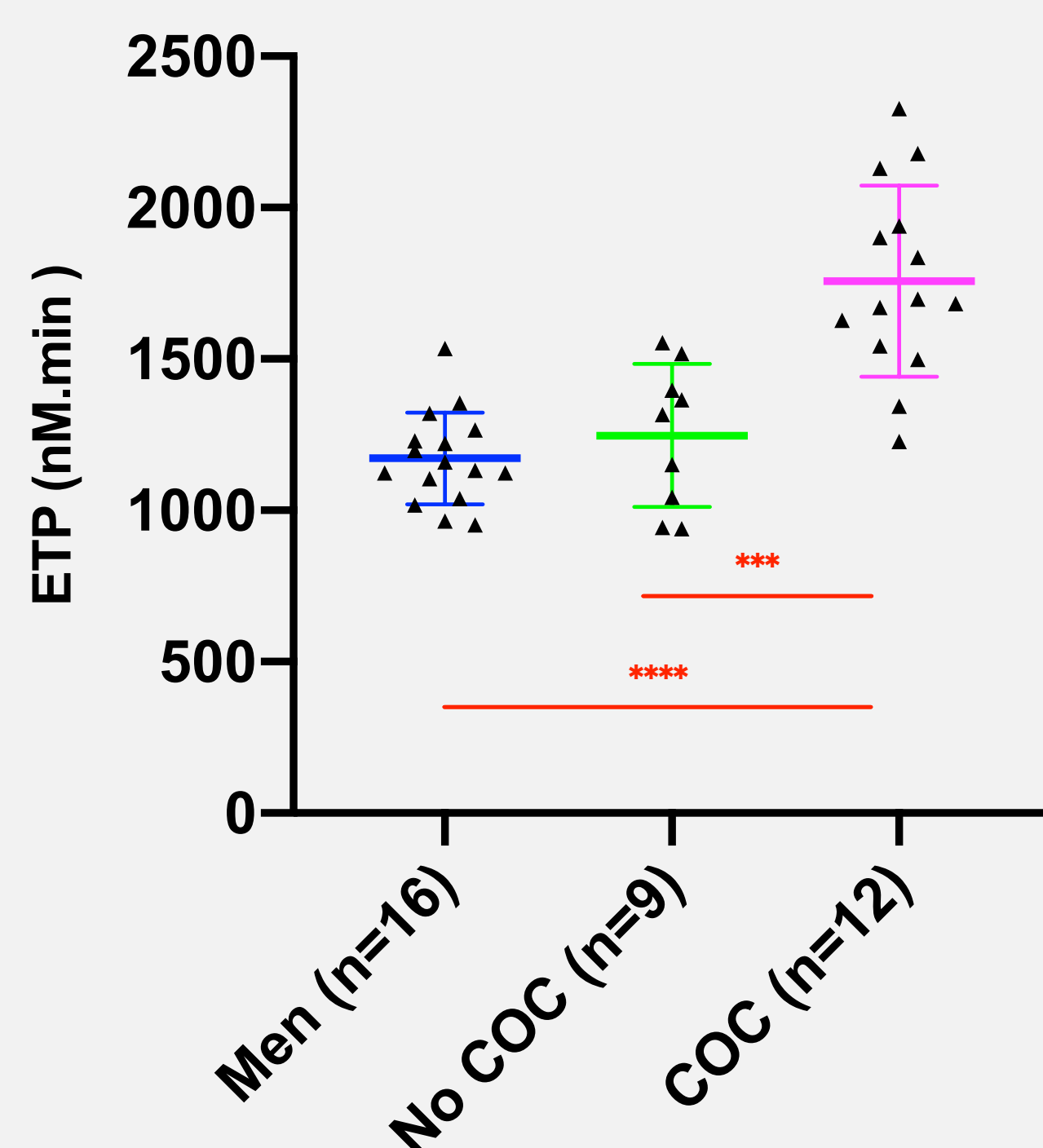


Figure 1 : Mean ETP \pm SD of men, women not using hormonal contraception (no COC) and women using COC (2nd and 3rd generation mixed).
*** p-value < 0.001; **** p-value < 0.0001.

- ❖ **In presence of APC**
 - We observed a higher resistance to APC in women not using hormonal contraception compared to men which was even more pronounced in women taking 2nd and 3rd COC.
 - Graphically, the AUC below the red curves (+APC) in women taking COC (2nd and 3rd generation) are higher compared to men and women not using hormonal contraception. [► Figure 2]

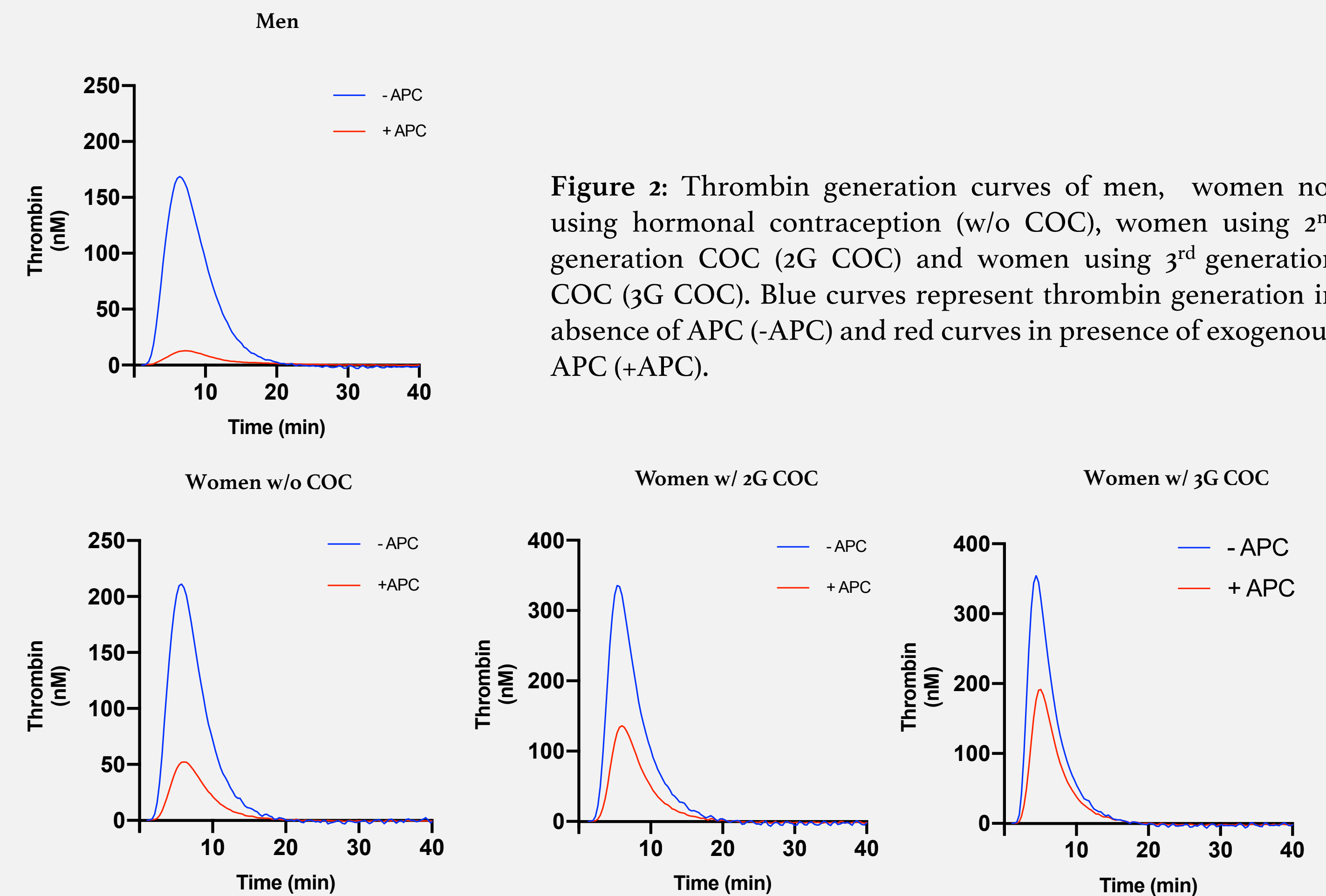


Figure 2 : Thrombin generation curves of men, women not using hormonal contraception (w/o COC), women using 2nd generation COC (2G COC) and women using 3rd generation COC (3G COC). Blue curves represent thrombin generation in absence of APC (-APC) and red curves in presence of exogenous APC (+APC).

B. Inhibition %

- ❖ Mean inhibition % (\pm SD) of men and women not using hormonal contraception were 92% (\pm 4%) and 75% (\pm 10%) (p-value < 0.0001)
- ❖ Mean inhibition % (\pm SD) of 2nd generation COC users and 3rd generation COC users were 61% (\pm 20%) and 45% (\pm 7%) respectively.
- ❖ Compared to men, differences were significant (p-value < 0.0001) and compared to women not using COC, the difference was significant only in women using 3rd generation COC (p-value = 0.001). [► Figure 3]

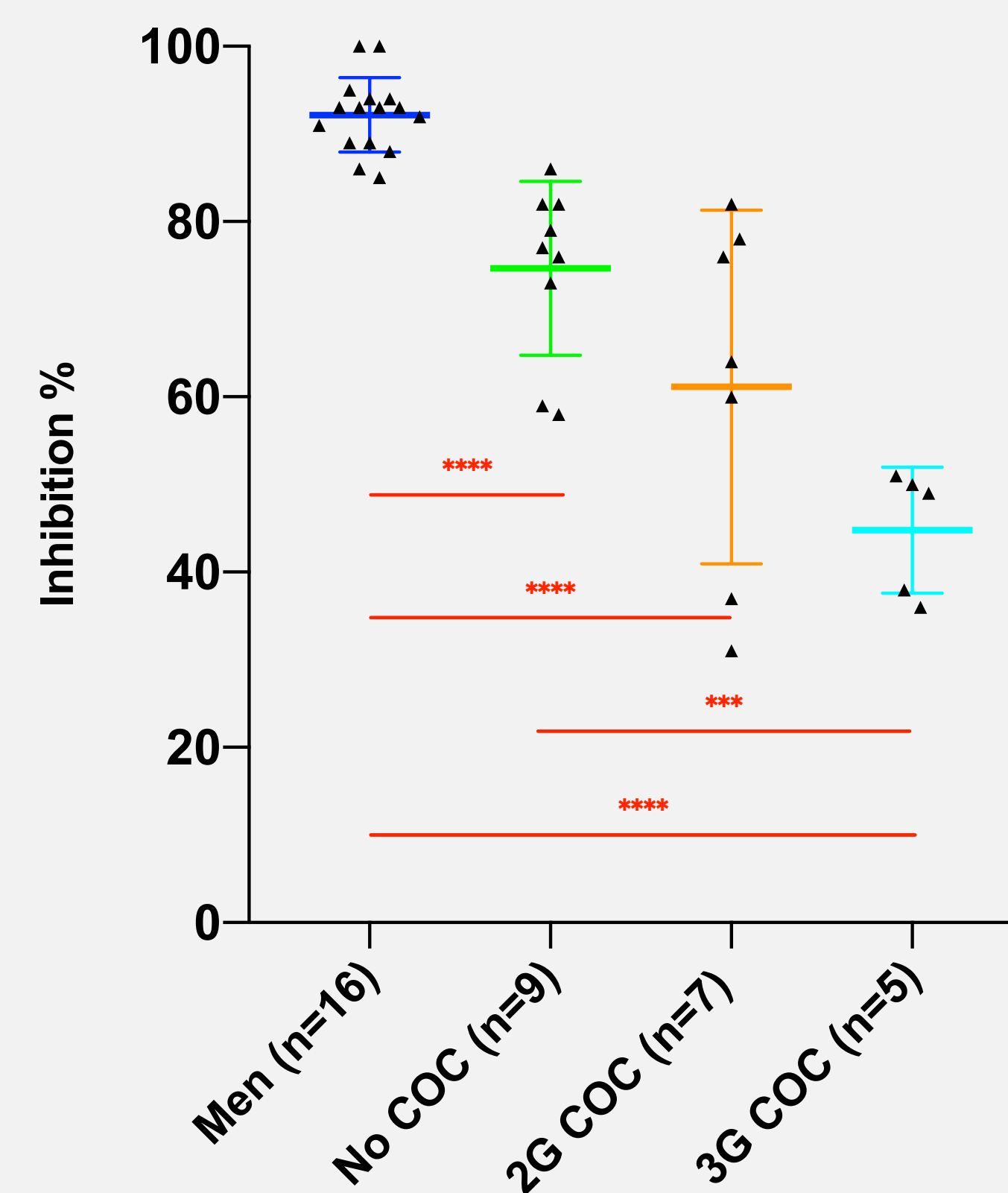


Figure 3 : Inhibition % of the ETP of men, women not using hormonal contraception (no COC), women using 2nd generation COC (2G COC) and women using 3rd generation COC (3G COC).
*** p-value < 0.001; **** p-value < 0.0001

- ❖ A trend towards a significant difference between 2nd and 3rd COC generation was observed but our pilot study was not sufficiently powered and was not designed for this endpoint. [► Figure 3]
- ❖ We estimated at 24 the number of women (12 using 2nd generation COC and 12 using 3rd generation COC) needed likely to observe significant difference between subgroups.

CONCLUSION

This newly validated APC resistance test is sensitive to differentiate men from women not using hormonal contraception, and can also differentiate different levels of APC resistance based on the type of COC.

The availability of a universal assay for evaluating ETP-based APC resistance is welcome and will finally allow study-to-study comparison in order to assess the APC resistance in different populations.

The implementation of this validated assay in routine can also identify subjects with higher absolute risk at baseline, which may help the physician regarding his prescription choices.

Conflict of Interest :

Jonathan Douxflis reports personal fees from Daiichi Sankyo, Diagnostica Stago, Roche and Roche Diagnostics outside the submitted work. Jonathan Douxflis is the CEO and founder of QUALIblood s.a.

References:

- ¹ Guideline on clinical investigation of steroid contraceptives in women - EMEA/CPMP/EWP/519/98 Rev 1.
- ² Nicolaes GA, Thomassen MC, Tans G, Rosing J, Hemker HC. Effect of activated protein C on thrombin generation and on the thrombin potential in plasma of normal and APC-resistant individuals. *Blood Coagul Fibrinolysis*. 1997; 8: 28-38.